REMARKS

Claims 1-5 are pending in the application.

Claim 1 has been revised to use alternative language directed to the same subject matter. No change in claim scope is intended or believed to have occurred. Support for the revisions to the claim is provided at least by the claim as previously presented.

Claims 2-4 have been revised to correct a clerical error.

No new matter has been introduced, and no issue requiring new search or consideration has been raised. Entry of the revised claims is respectfully requested.

Alleged Rejection Under 35 U.S.C. 112, first paragraph

Claims 1-5 were rejected under 35 U.S.C. 112, first paragraph as allegedly failing to be supported by an enabling description. Applicants have carefully reviewed the statement of the rejection as well as its history and respectfully traverse because no prima facie case of non-enablement is present. Reconsideration and withdrawal of the instant rejection is respectfully requested.

The statement of the rejection begins by acknowledging that the specification enables transfecting fibroblasts with DNA encoding TGF-β1 operably linked to a promoter, and transplanting the transfected fibroblasts into a mammalian joint space to generate hyaline cartilage.

But the rejection is based upon multiple allegations. They are summarized as follows in the order presented in the Action mailed March 1, 2007.

Allegation #1: The specific combination of vector, cell, and mode of delivery is unpredictable (see pages 4-6 of the Action).

Allegation #2: The specification does not enable using the claimed invention to treat osteoarthritis (see pages 6-7 of the Action).

Allegation #3: The specification does not enable the replacement of TGF-β1 by BMP-2 (see page 7 of the Action).

Allegation #4: The specification does not enable the replacement of TGF-β1 transfected fibroblasts by the use of chondrocytes (see pages 7-8 of the Action).

Before addressing the above allegations in detail, Applicants point out the well established standard that an application **must** be taken as presumptively enabling unless there is objective reason to doubt the statements contained therein (see MPEP 2164.04 and the case

decisions cited therein, such as *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)). This presumption is present before any "determination of enablement" is to occur under the *In re Wands* factors.

And while the level of predictability/unpredictability is one of the *Wands* factors, Applicants point out that the presence of unpredictability alone is insufficient to establish a *prima facie* case of non-enablement. Instead, a demonstration of undue experimentation is necessary. It is also well settled that the presence of enablement does not mean the lack of experimentation. To the contrary, routine and/or repetitive experimentation is the opposite of undue experimentation and is clearly permitted as evident from the facts of *In re Wands*.

Based on these standards, Applicants respectfully submit that no objective reason has been provided to doubt the presumption of enablement in the pending claims **and** no more than routine and/or repetitive experimentation is needed to make and use the claimed invention.

With respect to Allegation #1, Applicants point out that the discussion and documents cited on pages 4-6 of the Action appear to only reflect an assertion of unpredictability being present in gene therapy. But the presence of unpredictability alone is insufficient to support a rejection alleging non-enablement. Instead, the question is whether undue experimentation is necessary to transfect chondrocytes to express TGF-β1 or BMP-2 and transplant the transfected cells to a mammalian host's joint space to regenerate hyaline cartilage.

But the instant rejection raises no question regarding the skilled person's ability to transfect chondrocytes with TGF-β1 or BMP-2. There is also no question as to the ability to transplant the transfected cells. There is only the allegation that many publications discuss the unpredictability present in gene therapy, *where none of those publications discuss transfecting chondrocytes to express TGF-β1 and BMP-2 and transplantation of the transfected chondrocytes to a mammalian joint space to produce hyaline cartilage*. Indeed, the cited documents do not discuss unusual or abnormal unpredictability in transfecting chondrocytes or recombinantly expressing TGF-β1 or BMP-2.

There is no undue experimentation in the components of the methods as claimed. Specifically, there is no undue experimentation to generate the nucleic acid molecule for transfection, to transfect chondrocytes *in vitro*, or to transplant the transfected chondrocytes into a mammalian joint space. Therefore, there is no objective reason to doubt that a skilled person in the field is able to make and use these underlying components of the claimed methods without undue experimentation. Indeed, U.S. Patent 6,797,703 (cited below with

respect to an allegation of obviousness-type double patenting) discloses and claims the injecting of chondrocytes, transfected with TGF-β1, into a mammalian joint space to generate hyaline cartilage.

In light of the presence of enablement for the underlying components, Allegation #1 is no more than an attempt to doubt the **presumption** of enablement for the claimed methods to regenerate hyaline cartilage in a mammalian joint space. But the attempt is deficient because there is no objective reason to doubt that chondrocytes transfected to express TGF-β1 or BMP-2 will regenerate hyaline cartilage in a mammalian joint space.

The inadequate nature of Allegation #1 is seen in the assertion that "[t]he specification does not establish chondrocytes provide the same affinity or amount of expression as fibroblasts" (see page 9, second full paragraph, of the Action). But it is well settled that working examples are not absolutely necessary to support enablement (see the standard set out at MPEP 2164.02 and the case decisions cited therein). To the contrary, the burden is on the part of the Office to provide objective reasons to doubt the presumption that chondrocytes would function in the same manner as demonstrated for fibroblasts. No such reasons have been presented.

Additionally, and even if such reasons were present, the instant rejection fails to establish how undue experimentation is needed to make and use the methods to regenerate hyaline cartilage. Applicants respectfully submit that every component of the claimed methods can be made without undue experimentation, and so there is no undue experimentation in combining the components in the manner as claimed.

With respect to Allegation #2, Applicants point out that the claims have been revised to include the feature that the mammalian host is afflicted with osteoarthritis. Because there is no objective reason to doubt the ability to regenerate hyaline cartilage in a mammalian joint space for the reasons explained above, there is similarly no objective reason to doubt that regeneration of the cartilage would also occur in a mammalian host afflicted with osteoarthritis.

The assertions on pages 6-7 of the Action include the allegation that rabbit models used in the working examples of the instant application are "not art-accepted models for osteoarthritis; nor do the rabbits correlate to osteoarthritis" (see page 6, last paragraph). But this is merely an improper attempt to replace the requirement for an objective reason by using Applicants own data against Applicants! If the rabbit model data were not present in the

instant application, there would be no objective reason to doubt the presumption of enablement. Therefore, the presence of the data (assumed to be inadequate for the purposes of argument) **cannot** be an objective reason to doubt the presumption.

Finally, where is the undue experimentation in transplanting transfected chondrocytes to mammals afflicted with osteoarthritis as claimed? As explained above, there is no undue experimentation in the components of generating the nucleic acid molecule for transfection, of transfecting chondrocytes, or of transplanting into a joint space. Additionally, there is no undue experimentation in identifying mammals with osteoarthritis. Therefore, there is no undue experimentation needed to make and use the claimed methods.

Turning to Allegation #3, the statement of the rejection is based upon assertions that "the specification does not correlate the function of TGF-β1 to BMP-2 such that cartilage could be regenerated" (see page 7, first full paragraph, of the Action). But this is clearly an improper requirement for actual demonstration of a working example using BMP-2. As explained above, there is no requirement for a working example as necessary to support enablement. Therefore, this allegation is misplaced and clearly does not support the instant rejection.

Last, Allegation #4 is clearly improper because the use of transfected fibroblasts and chondrocytes in similar contexts is known to the skilled person. For example, U.S. Patent 6,315,992 discloses, and claims, the injecting of fibroblasts (transfected with TGF-β1) into a mammalian joint space to generate hyaline cartilage.

In a related manner, and as noted above, U.S. Patent 6,797,703 discloses and claims the injecting of chondrocytes, also transfected with TGF-β1, into a mammalian joint space to generate hyaline cartilage.

In light of these documents, Allegation #4 is clearly misplaced and should be withdrawn.

In light of the foregoing, Applicants respectfully submit that no *prima facie* case of non-enablement is present, and this rejection may be properly withdrawn.

Alleged Rejection Under 35 U.S.C. 112, second paragraph

Claims 2-5 were rejected as allegedly indefinite for dependence from canceled claim 13. Applicants have corrected this clerical error in the revised claims as presented above. Therefore, this rejection may be properly withdrawn.

Alleged Obviousness-Type Double Patenting

Claims 1-5 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-11 of U.S. Patent No. 6,797,703 (application number 09/702,718, which claims benefit of priority to application number 09/345,415, now USP 6,315,992). Applicants point out that the instant application also claims benefit of priority to 09/345,415.

Without acquiescence to this rejection, Applicants submit herewith an executed Terminal Disclaimer to obviate this rejection. Therefore, this rejection may be properly withdrawn.

Conclusion

It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is authorized to charge JHK Law's Deposit Account No. **502486** for any fees required under 37 CFR §§ 1.16 and 1.17 that are not covered, in whole or in part, by a credit card payment enclosed herewith and to credit any overpayment to said Deposit Account No. **502486**.

Respectfully submitted,

JHK Law

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